

REMARKS

Claims 48-100 and 102-182 were previously pending in this application. All of the previously pending claims have been canceled in favor of new claims 183-376 added above. Accordingly, claims 183-376 are being presented for further examination on the merits.

At the very outset, acknowledgement and appreciation is made of the courtesy extended by Examiner Ardin H. Marschel, Ph.D. in the personal interview held on March 23, 1999 with Dr. Dean L. Engelhardt, the Senior Vice President for the instant assignee, and the undersigned attorney. The presentation of the new claims hereinabove are in large part a response to the discussion held at the March 23, 1999 interview.

The title of the invention has been changed. The new title is believed to be a better reflection of the subject matter embraced by this application. In addition, some minor informalities in the disclosure regarding the correct spelling for the generic name for TRITON X-100 have been corrected on pages 18, 24 and 25 in the specification.

New claims 183-376 have been added above in place of the former claims which have been canceled. The new claims are directed to the following subject matter:

- a composition of matter comprising a transparent non-porous or translucent non-porous system containing a fluid or solution (claims 183-230);
- a composition of matter comprising a transparent non-porous or translucent non-porous system containing a fluid or solution, which system comprises a double-stranded oligonucleotide or polynucleotide which is directly or indirectly fixed or immobilized to said system (claims 231-270);
- a transparent non-porous or translucent non-porous system containing a fluid or solution (claims 271-318) or capable of retaining or containing a fluid or solution (claims 375-376);

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<u>New Claim</u>	<u>Subject Matter</u>	<u>Cross-Reference to Former/Original Claims or Disclosure/Comments</u>
188	non-porous solid support is selected from . . . siliceous matter and non-porous polymeric material	same as former claim 53
189	siliceous matter comprises glass or glass-coated surface	same as former claim 54
190	glass or glass-coated surface comprises porous glass	same as former claim 133
191	non-porous polymeric material comprises plastic or a plastic-coated surface	same as former claim 135
192	plastic or plastic-coated surface is selected from . . . polyethylene, polypropylene, polystyrene and polyepoxide	same as former claim 55 except "epoxy" has been changed to "polyepoxide"
193	system is selected from . . . a well, a <u>depression</u> , a tube, a cuvette and a <u>collection or set</u> of said wells, <u>depressions</u> , tubes and cuvettes	same as former claim 56 except that "depression" & "depressions" have been added (see spec. p. 16, line 11) "collection or set" also added in place of "apparatus" and "plurality"
194	said well comprises a microtiter well	same as former claim 57
195	said wells in the collection or set comprise microtiter wells	same as former claim 58 except that "collection or set added in place of apparatus
196	system is selected from . . . a well, a <u>depression</u> , a tube, a cuvette and a <u>collection or set</u> of said wells, <u>depressions</u> , tubes and cuvettes, and said solid support is selected from . . . dextran, cellulose, nitrocellulose, glass or a glass-coated surface and plastic or a plastic-coated surface	same as former claim 138 except "depression," "depressions" & "collection or set" have been added (see claim 193 above)
197	said solid support and said system are composed of the same materials	same as former claim 59
198	said solid support and said system are composed of different materials	same as former claim 60

<u>New Claim</u>	<u>Subject Matter</u>	<u>Cross-Reference to Former/Original Claims or Disclosure/Comments</u>
199	said solid support and said system are the same	original claim 20 [see also Engelhardt Decl. & 7/21/98 Amendment (pages 18-21)]
200	said system functions as the solid support	same as former claim 140
201	one of said oligonucleotide or polynucleotide strands is directly or indirectly fixed or immobilized to the solid support	same as former claim 61
202	said oligonucleotide or polynucleotide strands is fixed or immobilized to the solid support by sandwich hybridization	same as former claim 62 except that "directly" has been deleted
203	said double-stranded oligonucleotide or polynucleotide is selected from . . . DNA, RNA and a DNA-RNA hybrid	same as former claim 63 except that "or a combination of any of the foregoing" has been deleted
204	one of said strands comprises a nucleic acid sequence sought to be identified or quantified	spec., <i>inter alia</i> , p. 1, 2nd full ¶
205	said nucleic acid sequence sought to be identified or quantified comprises a member selected from . . . gene or gene sequence, a pathogen or pathogenic sequence, an oncogene, and a combination of any of the foregoing. . .	see Ward et al., EP 63879 (cited in spec., pages 7-8)
206	any of said members comprises a mutation selected from . . . deletion, an insertion, an inversion, a point mutation, and a combination of any of the foregoing	see Ward et al., EP 63879 (cited in spec., pages 7-8)
207	said oligonucleotide or polynucleotide is partially double-stranded	spec., Examples 1-7
208	said label or labels are the signaling entity or entities	same as former claim 64 except that "moiety or moieties" have been changed to "entity or entities"

<u>New Claim</u>	<u>Subject Matter</u>	<u>Cross-Reference to Former/Original Claims or Disclosure/Comments</u>
209-210	said label or labels are directly attached . . . to the oligonucleotide or polynucleotide	same as former claim 65
211-212	said label or labels are indirectly attached . . . to the oligonucleotide or polynucleotide	same as former claim 66
213-214	said label or labels are indirectly attached . . . through the formation of a complex	same as former claim 67
215-216	said complex is selected from . . . biotin and avidin, biotin and streptavidin, a sugar and a lectin, and an antigen and an antibody	same as former claim 68
217-218	said indirect attachment . . . is through a bridging moiety	same as former claim 69 except for minor wordsmithing
219	signaling entity or entities of said label or labels are directly or indirectly attached . . .	same as former claim 70 except for "moiety or moieties" → "entity or entities (see claim 208 above)
220	said signaling entity or entities are directly produced	derived from former claims 71-72, 94-95 & 126-127
221	said signaling entity or entities are selected from . . . chromagen, fluorescence and chemiluminescence	same as former claim 72 except for "signaling entity or entities" in place of "soluble signal"
222	said signaling entity or entities are selected from . . . enzyme, a co-enzyme, a chelating compound, a chromagen, a fluorescent compound and a chemiluminescent compound	same as former claim 71 except "compound" inserted for "agent" and "moiety or moieties" → "entity or entities"
223	said signaling entity or entities are selected from . . . a colored compound, a chemiluminescent compound and a fluorescent compound	same as former claim 76 except "compound" inserted for "product" and "signaling entity or entities" inserted for "soluble signal"

<u>New Claim</u>	<u>Subject Matter</u>	<u>Cross-Reference to Former/Original Claims or Disclosure/Comments</u>
224	said colored compound comprises a dye	see Ward et al., EP 63879 (cited in spec., pages 7-8)
225	wherein said chemical label or labels comprise self-indicating signaling entities	follows language in former independent claim 48 and the addition of "self-indicating"
226	wherein said self-indicating signaling entities are selected from . . . a fluorescent compound, a chemiluminescent compound and a chromagen compound, and a combination of any of the foregoing	derived from former claim 71 except that "agent" has been changed to "compound" and "signaling moiety or moieties" is now "self-indicating signaling entities"
227	said signaling entity or entities are indirectly produced or generated	derived from former claim 73 except for deletion of "enzyme or enzymatic reaction" & change from "soluble signal" to "signaling entity or entities"
228	said signaling entity or entities are indirectly generated or generatable by an enzyme or enzymatic reaction	same as former claim 73 except "soluble signal" changed to "signaling entity or entities"
229	said signaling entity or entities are detectable or quantifiable by a technique selected from . . . photometric techniques and colorimetric techniques	same as former claim 74 except "soluble signal" changed to "signaling entity or entities; quantifiable also added
230	said photometric techniques comprise spectrophotometric techniques	same as former claim 75

<u>New Claim</u>	<u>Subject Matter</u>	<u>Cross-Reference to Former/Original Claims or Disclosure/Comments</u>
231	A composition of matter comprising a transparent non-porous or translucent non-porous system containing a fluid or solution, . . . comprises: a double-stranded oligonucleotide or polynucleotide which is directly or indirectly fixed or immobilized to said system; and a chemical label or labels attached to one of said strands, <u>said label or labels comprising a signaling entity or entities</u> which are quantifiable in or from said fluid or solution or in or through said system, <u>said quantity being proportional to the amount or quantity of said label or labels</u>	derived from former claim 77 connection provided between labels and signaling entities per suggestions of 3/23/99 interview
232	said non-porous system is selected from . . . siliceous matter and non-porous polymeric material	same as former claim 78
233	said siliceous matter comprises glass or a glass-coated surface	same as former claim 79
234	said glass or glass-coated surface comprises porous glass	same as former claim 133
235	said non-porous polymeric material comprises plastic or a plastic-coated surface	same as former claim 136
236	said plastic or plastic-coated surface is selected from . . . polyethylene, polypropylene, polystyrene and polyepoxide	same as former claim 80 except "epoxy" changed to "polyepoxide"
237	said system is selected from . . . a well, a depression, a tube, a cuvette and a collection or set that comprises said wells, depressions, tubes and cuvettes	same as former claim 81 except that "plurality" was changed to "set or collection"; also "depression" & "depresssions" added
238	said well comprises a microtiter well	same as former claim 82
239	said wells in the collection or set comprise microtiter wells	same as former claim 83 except "apparatus" has been changed to "collection or set"

<u>New Claim</u>	<u>Subject Matter</u>	<u>Cross-Reference to Former/Original Claims or Disclosure/Comments</u>
240	wherein said system functions as a solid support	same as former claim 141
241	wherein one of said oligonucleotide or polynucleotide strands is directly or indirectly fixed or immobilized to said system	same as former claim 84
242	wherein said oligonucleotide or polynucleotide strand is directly or indirectly fixed or immobilized to said system by sandwich hybridization	same as former claim 85 except "directly" has been deleted
243	wherein said double-stranded oligonucleotide or polynucleotide is selected from . . . DNA, RNA and a DNA-RNA hybrid	same as former claim 86 except that "or a combination of any of the foregoing" has been deleted
244	wherein one of the strands comprises a nucleic acid sequence sought to be identified or quantified	spec., <i>inter alia</i> , p. 1 2nd full ¶
245	said nucleic acid sequence sought to be identified or quantified comprises a member selected from . . . gene or gene sequence, a pathogen or pathogenic sequence, an oncogene, and a combination of any of the foregoing.	see Ward et al., EP 63879 (cited in spec., pages 7-8)
246	any of said members comprises a mutation selected from . . . deletion, an insertion, an inversion, a point mutation, and a combination of any of the foregoing	see Ward et al., EP 63879 (cited in spec., pages 7-8)
247	wherein said oligonucleotide or polynucleotide is partially double-stranded	spec., Exs. 1-7
248	wherein said label or labels are the signaling entity or entities	same as former claim 87 except "signaling moiety or moieties" changed to "signaling entity or entities"
249-250	wherein said label or labels are directly attached to the oligonucleotide or polynucleotide	same as former claim 88

<u>New Claim</u>	<u>Subject Matter</u>	<u>Cross-Reference to Former/Original Claims or Disclosure/Comments</u>
251-252	said label or labels are indirectly attached to the oligonucleotide or polynucleotide	same as former claim 89
253-254	said label or labels are indirectly attached . . . through the formation of a complex	same as former claim 90
255-256	said complex is selected from . . . biotin and avidin, biotin and streptavidin, a sugar and a lectin, and an antigen and an antibody	same as former claim 91
257-258	said indirect attachment . . . is through a bridging moiety	same as former claim 92 except for minor word-smithing
259	signaling entity or entities of said label or labels are directly or indirectly attached thereto	same as former claim 93 except "signaling moiety or moieties" changed to "signaling entity or entities"
260	said signaling entity or entities are directly produced	derived from former claims 71-72, 94-95 & 126-127
261	said signaling entity or entities are selected from . . . chromagen, fluorescence and chemiluminescence	same as former claim 95 except for "signaling entity or entities" inserted for "soluble signal" and "is generatable from" was changed to "are selected from . . ."
262	said signaling entity or entities are selected from . . . enzyme, a co-enzyme, a chelating compound, a chromagen, a fluorescent compound and a chemiluminescent compound	same as former claim 94 except "compound" inserted for "agent" and "moiety or moieties" → "entity or entities"
263	said signaling entity or entities are selected from . . . a colored compound, a chemiluminescent compound and a fluorescent compound	same as former claim 99 except "moiety or moieties" → "entity or entities" and "compound" inserted for "product"
264	said colored compound comprises a dye	see Ward et al., EP 63879 (cited in spec., pages 7-8)

<u>New Claim</u>	<u>Subject Matter</u>	<u>Cross-Reference to Former/Original Claims or Disclosure/Comments</u>
265	wherein said chemical label or labels comprise self-indicating signaling entities	follows language in independent claim 77 except for addition of "self-indicating"
266	wherein said self-indicating signaling entities are selected from . . . a fluorescent compound, a chemiluminescent compound and a chromagen compound, and a combin- ation of any of the foregoing	derived from former claim 94 except that "agent" has been changed to "compound"
267	said signaling entity or entities are indirectly produced or generated	derived from former claim 96 except for deletion of "enzyme or enzymatic reaction"
268	said signaling entity or entities are indirectly generated or generatable by an enzyme or enzymatic reaction	same as former claim 96 except "soluble signal" was changed to "signaling entity or entities"
269	said signaling entity or entities are detect- able or quantifiable by a technique selected from . . . photometric techniques and color- imetric techniques	same as former claim 97 except "soluble signal" has been changed to signaling entity or entities" and "quantifiable" has been added
270	said photometric techniques comprise spectrophotometric techniques	same as former claim 98

<u>New Claim</u>	<u>Subject Matter</u>	<u>Cross-Reference to Former/Original Claims or Disclosure/Comments</u>
271	<p>A transparent non-porous or translucent non-porous system containing a fluid or solution, which system comprises:</p> <p>(i) a double-stranded nucleic acid comprising an oligonucleotide or polynucleotide hybridized or hybridizable to an oligo- or polynucleotide sequence;</p> <p>(ii) a chemical label or labels attached to one of said strands, said chemical label or labels comprising a signaling entity or entities which are quantifiable in or from said fluid or solution or in or through said system, <u>said quantity being proportional to the amount or quantity of said label or labels</u>; and</p> <p>(iii) a solid support having directly or indirectly fixed or immobilized thereto said oligo- or polynucleotide sequence or said oligonucleotide or polynucleotide</p>	<p>same as former claim 102</p> <p>per suggestions of 3/23/99 interview</p>
272	said solid support is contained within the transparent non-porous or translucent non-porous system	same as former claim 103
273	said solid support is porous or non-porous	same as former claim 104
274	said porous solid support comprises a porous polymeric material	same as former claim 105
275	porous polymeric material is selected from . . . dextran, cellulose and nitrocellulose	same as former claim 106
276	non-porous solid support is selected from . . . siliceous matter and non-porous polymeric material	same as former claim 107
277	siliceous matter comprises glass or a glass-coated surface	same as former claim 108
278	glass or glass-coated surface comprises porous glass	same as former claim 134
279	non-porous polymeric material comprises plastic or a plastic-coated surface	same as former claim 137
280	plastic or plastic-coated surface is selected from . . . polyethylene, polypropylene, polystyrene and polyepoxide	same as former claim 109 except "epoxy" changed to "polyepoxide"

<u>New Claim</u>	<u>Subject Matter</u>	<u>Cross-Reference to Former/Original Claims or Disclosure/Comments</u>
281	system is selected from . . . a well, a <u>depression</u> , a tube, a cuvette and a <u>a collection or set</u> of said wells, <u>depressions</u> , tubes or cuvettes	same as former claim 110 "depression" added (see spec. p. 16, line 11) "collection or set" added in place of "plurality" See claims 193 & 237 above
282	said well comprises a microtiter well	same as former claim 111
283	said wells in the collection or set comprise microtiter wells	same as former claim 58 except "apparatus" has been changed to "collec- tion or set"
284	system is selected from . . . a well, a depression, a tube, a cuvette and a collection or set of said wells, de- pressions, tubes or cuvettes, and said solid support is selected from . . . dextran, cellulose, nitrocellulose, glass or a glass-coated surface and plastic or a plastic-coated surface	same as former claim 138 except "depression" has been added (see claim 193 above)
285	said solid support and said system are composed of the same materials	same as former claim 59
286	said solid support and said system are composed of different materials	same as former claim 60
287	said solid support and said system are the same	original claim 20 [see also Engelhardt Decl. & 7/21/98 Amendment (pages 18-21)]
288	said system functions as the solid support	same as former claim 142
289	one of said oligonucleotide or polynucleotide strands is directly or indirectly fixed or immobilized to the solid support	same as former claim 61
290	said oligonucleotide or polynucleotide strands is fixed or immobilized to the solid support by sandwich hybridization	same as former claim 62 except that "directly" has been deleted
291	said double-stranded oligonucleotide or polynucleotide is selected from . . . DNA, RNA and a DNA-RNA hybrid	same as former claim 63 except that "or a combin- ation of any of the fore- going" has been deleted

<u>New Claim</u>	<u>Subject Matter</u>	<u>Cross-Reference to Former/Original Claims or Disclosure/Comments</u>
292	one of said strands comprises a nucleic acid sequence sought to be identified or quantified	spec., <i>inter alia</i> , p. 1 2nd full ¶
293	said nucleic acid sequence sought to be identified or quantified comprises a member selected from . . . gene or gene sequence, a pathogen or pathogenic sequence, an oncogene, and a combination of any of the foregoing	Ward et al., EP 63879 (cited in spec., pages 7-8)
294	any of said members comprises a mutation selected from . . . deletion, an insertion, an inversion, a point mutation, and a combination of any of the foregoing	same as claim 293 above
295	said oligonucleotide or polynucleotide is partially double-stranded	spec., Exs. 1-7
296	said label or labels are the signaling entity or entities	same as former claim 64 except that "moiety or moieties" have been changed to "entity or entities"
297-298	said label or labels are directly attached to the oligonucleotide or polynucleotide	same as former claim 65
299-300	said label or labels are indirectly attached to the oligonucleotide or polynucleotide	same as former claim 66
301-302	said label or labels are indirectly attached . . . through the formation of a complex	same as former claim 67
308	said signaling entity or entities are directly produced	derived from former claims 71-72, 94-95 & 126-127
309	said signaling entity or entities are selected from . . . chromagen, fluorescence and chemiluminescence	same as former claim 72 except for "signaling entity or entities" in place of "soluble signal"
310	said signaling entity or entities are selected from . . . enzyme, a co-enzyme, a chelating compound, a chromagen, a fluorescent compound and a chemiluminescent compound	same as former claim 71 except "compound" inserted for "agent" and "moiety or moieties" → "entity or entities"

<u>New Claim</u>	<u>Subject Matter</u>	<u>Cross-Reference to Former/Original Claims or Disclosure/Comments</u>
311	said signaling entity or entities are selected from . . . a colored compound, a chemiluminescent compound and a fluorescent compound	same as former claim 76 except "compound" inserted for "product" and "signaling entity or entities" inserted for "soluble signal"
312	said colored compound comprises a dye	see Ward et al., EP 63879 (cited in spec., pages 7-8)
313	wherein said chemical label or labels comprise self-indicating signaling entities	follows language in former independent claim 48 and the addition of "self-indicating"
314	wherein said self-indicating signaling entities are selected from . . . a fluorescent compound, a chemiluminescent compound and a chromagen compound, and a combination of any of the foregoing	derived from former claim 71 except that "agent" has been changed to "compound"
315	said signaling entity or entities are indirectly produced or generated	derived from former claim 73 except for deletion of "enzyme or enzymatic reaction"
316	said signaling entity or entities are indirectly generated or generatable by an enzyme or enzymatic reaction	same as former claim 73 except "soluble signal" changed to "signaling entity or entities"
317	said signaling entity or entities are detectable or quantifiable by a technique selected from . . . photometric techniques and colorimetric techniques	same as former claim 74 except "soluble signal" changed to "signaling entity or entities; quantifiable also added"
318	said photometric techniques comprise spectrophotometric techniques	same as former claim 75

<u>New Claim</u>	<u>Subject Matter</u>	<u>Cross-Reference to Former/Original Claims or Disclosure/Comments</u>
319	<p>An apparatus comprising:</p> <ol style="list-style-type: none"> 1) one or more transparent non-porous or translucent non-porous devices for containing fluid or solution; 2) one or more surfaces or solid supports for fixing or immobilizing nucleic acids thereto, said one or more surfaces or solid supports being located in said one or more devices; 3) components for fixing or immobilizing nucleic acids of interest or sought to be identified; and 4) components for producing in or from a fluid or solution or in or through said device a quantifiable signal from a double-stranded nucleic acid, wherein one of said strands comprises a chemical label or labels which comprise a signaling entity or entities, said quantifiable signal being proportional to the amount or quantity of chemical labels attached to said nucleic acid 	<p>derived from former claims 100 & 132 with "means for" language deleted</p>
320	<p>An apparatus comprising:</p> <ol style="list-style-type: none"> 1) one or more transparent non-porous or translucent non-porous devices for containing fluid or solution, each such device comprising a surface or a solid support for fixing or immobilizing nucleic acid thereto; 2) components for fixing or immobilizing to said surfaces or solid supports a nucleic acid of interest or sought to be identified; and 3) components for producing in or from a fluid or solution or in or through said device a quantifiable signal from a double-stranded nucleic acid, wherein one of said strands comprises a chemical label or labels which comprise a signaling entity or entities, said quantifiable signal being proportional to the amount or quantity of chemical labels attached to said nucleic acid strand 	<p>derived from former claims 100 & 132 with "means for" language deleted</p>

<u>New Claim</u>	<u>Subject Matter</u>	<u>Cross-Reference to Former/Original Claims or Disclosure/Comments</u>
321	An apparatus comprising: 1) one or more transparent non-porous or translucent non-porous devices for containing fluid or solution and for fixing or immobilizing thereto a nucleic acid of interest or sought to be identified; 2) components for fixing or immobilizing to said device or devices a nucleic acid of interest or sought to be identified; and 3) components for producing in or from a fluid or solution or in or through said device a quantifiable signal from a double-stranded nucleic acid, wherein one of said strands comprises a chemical label or labels which comprise a signaling entity or entities, said quantifiable signal being proportional to the amount or quantity of chemical labels attached to said nucleic acid strand.	derived from former claims 100 & 132 with "means for" language deleted
322	further comprising means for measuring said quantifiable signal, said measuring means being selected from . . photometric instrumentation, spectrophotometric instrumentation and colorimetric instrumentation	spec., p. 13, last two paragraphs
323	further comprising washing means to separate any unhybridized nucleic acids or other unreacted components	spec., p. 16, 1st full ¶, for "washing" means
324	further comprising (a) means for measuring said quantifiable signal, said measuring means being selected from . . . photometric instrumentation, spectrophotometric instrumentation and colorimetric instrumentation; and (b) washing means to separate any unhybridized nucleic acids or other unreacted or excess components	spec., p. 13, last two paragraphs, spec., p. 16, 1st full ¶, for "washing" means

<u>New Claim</u>	<u>Subject Matter</u>	<u>Cross-Reference to Former/Original Claims or Disclosure/Comments</u>
325	An array of substrate surfaces, each substrate surface comprising at least one <u>double-stranded</u> nucleic acid fixed or immobilized thereto, wherein at least one strand comprises one or more <u>chemical labels</u> which comprise a <u>signaling entity or entities</u> which are <u>quantifiable or detectable</u> , and wherein at least one nucleic acid <u>strand</u> or a <u>sequence</u> therefrom in one of said substrate surfaces is <u>different</u> from at least one other nucleic acid strand or a sequence therefrom in another substrate surface	derived from former claim 143 reference added to: "double-stranded" "chemical labels" "signaling entity or entities" "quantifiable" "detectable" "different strand or sequence"
326	wherein each of said substrate surfaces has been treated with a surface treatment agent	derived from former claim 144 except for deletion of "enhance, fixation or immobilization" & addition of "surface treatment agent"
327	wherein said surface treatment agent comprises an amine or amide compound	same as former claim 145 except for addition of "surface treatment agent"
328	wherein said amine compound is selected from . . . duodecadiamine (DDA), polylysine (PPL) aminopropyltriethoxysilane and a combination of any of the foregoing	same as former claim 146 except "or" was changed to "and"
329	wherein said amide compound comprises formamide	same as former claim 147
330	wherein said surface treatment agent comprises a dispersive compound	derived from former claim 148 except "surface treatment agent" added and "is carried out" was changed to "comprises"
331	wherein said dispersive compound comprises ammonium acetate	same as former claim 149
332	wherein said surface treatment agent comprises an epoxy compound	derived from former claim 150 except "surface treatment agent" added

<u>New Claim</u>	<u>Subject Matter</u>	<u>Cross-Reference to Former/Original Claims or Disclosure/Comments</u>
333	said surface treatment agent is selected from . . . an amine compound and an epoxy compound	same as former claim 151
334	said substrate surface is porous or non-porous	same as former claim 152
335	said porous substrate surface comprises a porous polymeric material	same as former claim 153
336	said porous polymeric material is selected . . . dextran, cellulose and nitrocellulose	same as former claim 154
337	said non-porous substrate surface is selected from . . . siliceous matter and non-porous polymeric material	same as former claim 155
338	said siliceous matter comprises glass or a glass-coated surface	same as former claim 156
339	said glass or glass-coated surface comprises porous glass	same as former claim 157
340	said glass or glass-coated surface is selected from . . . wells, depressions, tubes and cuvettes	same as former claim 158 except for deletion of "apparatus . . ."
341	said wells comprise microtiter wells	same as former claim 159
342	said non-porous polymeric material comprises a plastic	same as former claim 160
343	said plastic is selected from . . . polyethylene, polypropylene, polystyrene and polyepoxide	same as former claim 161 except "epoxy" changed to "polyepoxide"
344	wherein one strand of each of said nucleic acid strands is fixed or immobilized directly or indirectly to said substrate surface	same as former claim 162 except reference to "one strand" added
345	said nucleic acid strands are single-stranded or double-stranded or partially double-stranded	same as former claim 163 except "partially double-stranded" added

<u>New Claim</u>	<u>Subject Matter</u>	<u>Cross-Reference to Former/Original Claims or Disclosure/Comments</u>
346	said nucleic acid strands are selected from . . . DNA, RNA and a DNA-RNA hybrid	same as former claim 164 except "or combinations thereof" deleted
347	said at least one nucleic acid strand comprises a nucleic acid sequence complementary to a nucleic acid sequence of interest or sought to be identified or quantified or sequenced	derived from former claim 170 except reference to "complementary," "of interest" & "quantified" has been added
348	said nucleic acid sequence of interest or sought to be identified or quantified or sequenced comprises a member selected from . . . a gene or gene sequence, a pathogen or pathogenic sequence, an oncogene, and a combination of any of the foregoing	see Ward et al., EP 63879 (cited in spec., pages 7-8)
349	wherein any of said members comprises a mutation selected from . . . a deletion, an insertion, an inversion, a point mutation, and a combination of any of the foregoing	same as claim 348 above
350	wherein said complementary nucleic acid sequence or sequences are unlabeled	same as former claim 166 except "complementary" has been added
351	said chemical label or labels are the signaling entity or entities	same as former claim 168 except that "chemical" has been added & "signaling moiety or moieties" has been changed to "signaling entity or entities"
352	said chemical label or labels comprise a signaling entity or entities which are quantifiable in or from a fluid or solution or in or through said substrate surfaces or a system containing said array or said substrate surfaces, <u>said quantity being proportional to the amount or quantity of quantity of said label or labels</u>	derived from former claim 167 except "soluble signal" deleted per suggestions of 3/23/99 interview

<u>New Claim</u>	<u>Subject Matter</u>	<u>Cross-Reference to Former/Original Claims or Disclosure/Comments</u>
353	said chemical label or labels comprise a signaling entity or entity which are quantifiable in or from a fluid or solution or in or through said substrate surfaces or a system containing said array or said substrate surfaces, <u>said quantity being proportional to the amount or quantity of said label or labels</u>	derived from former claim 167 except "soluble signal" deleted per suggestions of 3/23/99 interview
354	wherein the signaling entity or entities of said label or labels are directly attached thereto	same as former claim 169 except "signaling moiety or moieties" has been changed to "signaling entity or entities" & "indirectly" has been deleted
355	wherein the signaling entity or entities of said label or labels are indirectly attached thereto	same as former claim 169 except "signaling moiety or moieties" has been changed to "signaling entity or entities" & "directly" has been deleted
356	said label or labels are attached directly or indirectly to one or more nucleotides in said nucleic acid strands	same as former claim 171
357	said label or labels are attached directly or indirectly to one or more nucleotides in said nucleic acid strands	same as former claim 171
358	said label or labels are indirectly attached to one or more nucleotides through the formation of a complex	same as former claim 172
359	said label or labels are indirectly attached to one or more nucleotides through the formation of a complex	same as former claim 172
360	said complex is selected from . . . biotin and avidin, biotin and strept- avidin, a sugar and a lectin, and an antigen and an antibody	same as former claim 173

<u>New Claim</u>	<u>Subject Matter</u>	<u>Cross-Reference to Former/Original Claims or Disclosure/Comments</u>
361	wherein said complex is selected from . . . biotin and avidin, biotin and strept- avidin, a sugar and a lectin, and an antigen and an antibody	same as former claim 173
362	said label or labels are indirectly attached to one or more nucleotides through a bridging moiety	same as former claim 174
363	said label or labels are indirectly attached to one or more nucleotides through a bridging moiety	same as former claim 174
364	said signaling entity or entities are selected from the group consisting of an enzyme, a co-enzyme, a chelating agent, a chromagen agent, a fluorescent agent and a chemiluminescent agent	same as former claim 175 except that "signaling moiety or moieties" has been changed to "signal- ing entity or entities"
365	said signaling entity or entities are selected . . . an enzyme, a co-enzyme, a chelating agent, a chromagen agent, a fluorescent agent and a chemiluminescent agent	same as former claim 175 except that "signaling moiety or moieties" has been changed to "signal- ing entity or entities"
366	wherein a signal is generated or generatable from said chemical label or labels by a chromagen, or by fluorescence or chemiluminescence	same as former claim 176 except "soluble signal" changed to "signal gener- ated or generatable from said chemical label or labels"
367	wherein a signal is generated or generatable from said chemical label or labels by a chromagen, or by fluorescence or chemiluminescence	same as former claim 176 except "soluble signal" changed to "signal gener- ated or generatable from said chemical label or labels"
368	wherein a signal from said chemical label or labels is quantifiable or detectable by a technique selected from . . . photometric techniques and colorimetric techniques	same as former claim 177 except "soluble signal" changed to "signal from chemical label or labels"
369	wherein a signal from said chemical label or labels is quantifiable or detectable by a technique selected from . . . photometric techniques and colorimetric techniques	same as former claim 177 except "soluble signal" changed to "signal from chemical label or labels"

<u>New Claim</u>	<u>Subject Matter</u>	<u>Cross-Reference to Former/Original Claims or Disclosure/Comments</u>
370	wherein said photometric techniques comprise spectrophotometric techniques	same as former claim 178
371	wherein said photometric techniques comprise spectrophotometric techniques	same as former claim 178
372	said chemical label or labels are selected from . . . a colored compound, a chemiluminescent compound and a fluorescent compound	same as former claim 179 except "soluble signal" changed to "chemical label or labels"
373	said chemical label or labels are selected from . . . a colored compound, a chemiluminescent compound and a fluorescent compound	same as former claim 179 except "soluble signal" changed to "chemical label or labels" & "product" has been changed to "compound"
374	wherein said substrate surface is porous or non-porous	same as former claim 180 except that "apparatus" has been changed to "collection or set"
375	A transparent non-porous or translucent non-porous system capable of retaining or containing a fluid or solution, which system comprises the array of any of claims . . .	same as former claim 181 except for deletion of phrase "wherein said substrate surface is porous or non-porous"
376	wherein said substrate surfaces are contained within the transparent non-porous or translucent non-porous system	same as former claim 182 except for pluralization of substrate surface

Entry of the new claims 183-376 is respectfully requested.

ISSUES IN THE MARCH 23, 1999 INTERVIEW

Turning to other matters, the following issues were discussed at the March 23, 1999 interview:

1. proposals for further amending the independent former claims with respect to quantification;
2. "means for" language in the apparatus claims;

3. new matter issue in former claims 63, 86, 118, 146, 152, 164 and 180-182 with respect to "DNA, RNA, DNA-RNA hybrid, or a combination of any of the foregoing";
4. array claims; and
5. the "enhancement" language of former claims 144, 161 and 180-182.

1. **Proposed Amendments to Clarify Quantification in the Independent Claims**

As indicated above, each of the new claims 183, 231, 271 and 319-321 recite that "said quantifiable signal being proportional to the amount or quantity of said label or labels." This suggestion was discussed at the March 23, 1999 interview and has been incorporated into all of the independent claims presented above with the exception of claim 325 which is directed to an array of substrate surfaces. It is believed that the foregoing amendments will place the subject matter being claimed and pursued in a better condition for allowance.

2. **"Means For" Language in the Apparatus Claims**

New claims 319-321 are each directed to an apparatus in which no "means for" language is presented. To the extent that such language has been deleted, the apparatus claims are in better condition for allowance.

3. **New Matter Issue in Former Claims 63, 86, 118 & 164 ("DNA, RNA, DNA-RNA hybrid, or a combination of any of the foregoing")**

Former claims 63, 86, 118 and 164 have been replaced by new claims 203, 243, 291 and 346, respectively. None of the latter new claims recite the "combination" language extant in the former claims. To the extent that such language has been deleted, it is believed that claims 203, 243, 291 and 346 have been rendered in a better condition for allowance.

4. Array Claims

The new array claims are substantially changed from the former claims. All of the new array claims depend either directly or ultimately from new claim 325. The latter is directed to an array of substrate surfaces, each substrate surface comprising at least one double-stranded nucleic acid fixed or immobilized thereto. At least one strand comprises one or more chemical labels which comprise a signaling entity or entities which are quantifiable or detectable. Further, at least one nucleic acid strand or a sequence therefrom in one of the substrate surfaces is different from at least one other nucleic acid strand or a sequence therefrom in another substrate surface. The foregoing language is believed to clarify the subject matter which Applicants claim as part of their invention.

5. "Enhancement" Language of Former Claim 144-161 & 180-182

Former claims 144-161 and 180-182 contained language to the effect that each of said substrate surfaces has been treated to enhance fixation or immobilization to the surface. These claims have been canceled in favor of new claims 326-333. Claims 327-333 depend either directly or ultimately from claim 326 which is also dependent. Claim 326 recites that "each of said substrate surfaces has been treated with a surface treatment agent." The foregoing change reflected in the new claims is believed to clarify Applicants' claimed subject matter as well as to remove the ground of rejection. No issue of indefiniteness is presented with respect to enhancement of fixation or immobilization to the substrate surface.

ISSUES IN THE MARCH 16, 1999 OFFICE ACTION

Before closing, some reference should be made to the March 16, 1999 Office Action that was apparently issued without resort to Applicants' November 23, 1998 Second Supplemental Amendment which had not been entered into the file wrapper for the Examiner's consideration. Applicants and their attorney sincerely appreciate the opportunity to again address the issues presented in the

March 16, 1999 Office Action.

The following issues were presented in the March 16, 1999 Office Action:

- A. limitation in former claims 60 and 114 directed to the support and system being composed of different materials (Office Action, page 2, last paragraph);
- B. new matter in claims 63, 86, 118, 146, 152, 164 and 180-182 ("a combination of any of the foregoing" or "combinations thereof");
- C. new matter in claims 77-85, 87-99, 133, 136 and 141 (oligonucleotide or polynucleotide fixed or immobilized to the system rather than being fixed or immobilized to the solid support within such a system);
- D. new matter in claims 144-161 and 180-182 (enhancement of fixation or immobilization with several treatments including "a dispersive compound" of claim 148);
- E. anticipation rejection (Kourilsky et al., UK 2,019,408);
- F. anticipation rejection (Stuart et al., U.S. Patent No. 4,732,847);
- G. anticipation rejection (Langer-Safer et al. PNAS (1982) or Manuelidis et al. J. Cell Biology (1982));
- H. anticipation rejection (Ward et al., U.S. Patent No. 4,711,955);
- I. judicially created obviousness-type double patent over claim 17 of U.S. Patent No. 4,994,373; and
- J. informalities (specification, pages 18, 24 and 25 (correct spelling of the generic name for TRITON X-100 is "octoxymol" and not "octoxynol").

Taking the ten above-listed issues in order . . .

**A. Limitation in former claims 60 and 114 directed to the
support and system being composed of different materials**

Based upon the March 23, 1999 interview, it is Applicants' understanding that the rejection with respect to the support and system being composed of different materials has been withdrawn.

B. New matter in claims 63, 86, 118, 146, 152, 164 and 180-182 ("a combination of any of the foregoing" or "combinations thereof")

As indicated above, former claims 63, 86, 118 and 164 have been replaced by new claims 203, 243, 291 and 346, respectively. None of the latter new claims recite that the Markush group members also include "combinations" of DNA, RNA and a DNA-RNA hybrid. Thus, it is believed that this ground of rejection has been obviated by the presentation of the new claims.

C. New matter in claims 77-85, 87-99, 133, 136 and 141 (oligonucleotide or polynucleotide fixed or immobilized to the system rather than being fixed or immobilized to the solid support within such a system)

From the March 23, 1999 interview, Applicants understand that the rejection of claims 77-85, 87-99, 133, 136 and 141 as containing new matter has also been withdrawn. These claims have been canceled in favor of new claims 231-270.

D. New matter in claims 144-161 and 180-182 (enhancement of fixation or immobilization with several treatments including "a dispersive compound" of claim 148)

As noted both by the Examiner in the March 23, 1999 interview and in the March 16, 1999 Office Action, former claims 144-161 and 180-182 contained language to the effect that each of said substrate surfaces has been treated to enhance fixation or immobilization to the surface. These claims have been canceled in favor of new claims 326-333. New claim 326 recites that "each of said substrate surfaces has been treated with a surface treatment agent." The foregoing change reflected in the new claims is believed to clarify Applicants' claimed subject matter as well as to remove the ground of rejection.

- E. Anticipation rejection (Kourilsky et al., UK 2,019,408)
- F. Anticipation rejection (Stuart et al., U.S. Patent No. 4,732,847)
- G. Anticipation rejection (Langer-Safer et al. (1982) or Manuelidis et al. (1982))
- H. Anticipation rejection (Ward et al., U.S. Patent No. 4,711,955)

Various former claims were rejected for anticipation by the five documents listed above. It is Applicants' understanding that the claim amendments which were suggested at the March 23, 1999 and the November 3, 1998 interviews and have now been incorporated into the new independent claims, patentably distinguishes their claimed invention from any or all of the five cited disclosures.

- I. Rejection of claims 100, 102-108, 110-132, 134, 139 and 142-182
for judicially created obviousness-type double patenting over claim 17
of U.S. Patent No. 4,994,373

Applicants continue to maintain that their claimed invention is patentably distinct from the subject matter of claim 17 in U.S. Patent No. 4,994,373, issued on February 19, 1991. The previous double patenting rejection set forth in the March 12, 1998 Office Action was thoroughly addressed in Applicants' July 21, 1998 Amendment Under 37 C.F.R. §1.116 (pages 26-32). In the latest March 16, 1999 Office Action, the Examiner stated that "[i]t is noted that applicants' arguments have been persuasive for the instant composition claims but that claim 17 of the patent is a device which falls into the same restriction group as the above rejected claims."

At the outset, Applicants and the present Assignee wish to state their intention to maintain a line of demarcation between the present invention and the subject matter set forth in claim 17 of U.S. Patent No. 4,994,373. Such a demarcation line must necessarily take into consideration the restriction history in predecessor applications related to this application. In the June 13, 1984 restriction requirement issued by the Patent Office in U.S. Patent Application Serial

No. 06/461,969 (filed on January 27, 1983), the then pending claims were designated to contain five different and distinct inventions¹

The former claims that were rejected for obviousness-type double patenting over claim 17 (U.S. 4,994,373) included:

- claims 100, 132 (an apparatus) now new claims 321-324
- claims 102-131, 134, 139, 142 (a system)
now new claims 271-318 & 375-376
- claims 142-182 (an array of substrate surfaces)
now new claims 325-374

In the June 13, 1984 restriction requirement referred to above, the group of claims drawn to laboratory apparatus (classified in Class 422, subclass 99) was deemed to be different and distinct from the group of claims drawn to a device for measuring a chemical reaction (classified in Class 435, subclass 287). Furthermore, the group of claims drawn to a substrate to which a polynucleotide is fixed (classified in Class 435, subclass 188) was deemed in the same June 13, 1984 restriction requirement to be different and distinct from either of the afore-described apparatus or device groups. Thus, the present claims in the form of the compositions (substrate to which a polynucleotide is fixed) and apparatus could clearly be issued in the same patent without violating the substance or spirit of the June 13, 1984 restriction requirement, or the statutory provisions of 35 U.S.C. §121, rule related provisions of 37 Code of Federal Regulations and the Manual of Patent Examining Procedure. Moreover, the present composition and apparatus claims cannot be subject to the double patenting rejection because the Patent

¹ The five different and distinct invention groups were:

- I. Claims 1-11, 19-51, 69-71, 81-82, 85-86, 96-98, 100, 104-105, and 107-109, drawn to a substrate to which a polynucleotide is fixed, classified in Class 435, subclass 188.
- II. Claims 12-18, 52-62, 72, 74-80, 83-84, 87-95 and 99, drawn to an assay for detecting pathogens which utilizes nuclear hybridization(sic), classified in Class 435, subclass 6.
- III. Claims 64, 65, 68 and 73, drawn to laboratory apparatus, classified in Class 422, subclass 99.
- IV. Claims 63, 66-67, drawn to a coating process, classified in Class 427, subclass 299+.
- V. Claims 101-103 and 106, drawn to a device for measuring a chemical reaction, classified in Class 435, subclass 287.

Office has already deemed the instant subject matter to be different and patentably distinct from the subject matter of claim 17, U.S. 4,994,373.

With respect to the former array claims 143-182, now new claims 325-374, these claims clearly fall into Group I delineated in the June 13, 1984 restriction requirement because each defines a substrate to which a polynucleotide is fixed, classified in Class 435. Thus, the array claims clearly belong to the same group of claims represented by the present composition claims, 183-270.

In view of the foregoing remarks as well as their previous remarks on the double patenting rejection set forth in their June 21, 1998 Amendment, Applicants respectfully request that the rejection for obviousness-type double patenting be reconsidered and withdrawn, thereby placing each of new claims 183-376 in allowable condition.

J. Informalities [specification, pages 18, 24 and 25 (correct spelling of the generic name for TRITON X-100 is "octoxymol" and not "octoxynol")]

As indicated in the opening remarks of this paper, informalities have been corrected on three pages in the specification.

An early indication as to the allowable condition of new claims 183-376 is respectfully requested.

* * * * *

Stavrianopoulos et al.

Serial No.: 08/486,070

Filed: June 7, 1995

Page 60 [(Third Supplemental Amendment(Following Applicants' November 23, 1998
Second Supplemental Amendment - May 18, 1999)]

SUMMARY AND CONCLUSIONS

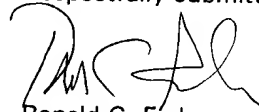
Claims 48-100 and 102-182 have been canceled in favor of new claims 183-376, the latter being presented for further examination.

The fee for adding new claims 183-376 is \$3066, based upon 166 additional new claims ($166 \times \$18 = \2988) and one new independent claim ($1 \times \$78 = \78). The Patent and Trademark Office is hereby authorized to charge the \$3,066 fee to Deposit Account 05-1135. No other fee is believed due in connection with this Third Supplemental Amendment, a three month extension fee having been previously authorized in connection with Applicants' July 21, 1998 Amendment Under 37 C.F.R. §1.115. In the event, however, that any other fee or fees are due in connection with this Third Supplemental Amendment or with any of Applicants' previous filings, The Patent and Trademark Office is hereby authorized to charge the amount of any such fee(s) to Deposit Account No. 05-1135, or to credit any overpayment thereto.

If it would be helpful to expediting the prosecution of this application, the undersigned may be contacted by telephone at 212-583-0100 during the daytime business hours.

Early and favorable action on this application is respectfully sought.

Respectfully submitted



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